P02.30 LB

Vectored ImmunoProphylaxis with VRC07 Protects BLT Humanized Mice from Vaginal Transmission of Founder HIV

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Background: Recently, a number of antibodies capable of broadly neutralizing HIV have been isolated from HIV infected patients, stimulating efforts to elicit their production in naive individuals. As an alternative to vaccination, we recently described vectored immunoprophylaxis (VIP) as an approach capable of generating high serum concentrations of a desired monoclonal antibody in mice following a single intramuscular injection of a specialized adeno associated viral vector (AAV). Mice that received VIP encoding b12, VRC01 or VRC07 antibodies demonstrated long-term circulating antibody expression in serum, and VIP-treated humanized mice exhibited remarkable protection against high dose, intravenous challenge with CXCR4-tropic HIV. However, most human infections are initiated by transmission of CCR5-tropic strains through mucosal tissues.
Methods: To measure the efficacy of VIP against clinically relevant strains, we humanized VIP-treated mice by adoptive transfer of peripheral blood mononuclear cells (PBMC) and challenged these animals with CCR5-tropic HIV strains including JR-CSF, as well as REJO.c, a transmitted molecular founder. To determine the ability of VIP to prevent mucosal transmission of clinically relevant HIV, we developed a repetitive intravaginal challenge model in VIP-treated BLT humanized mice that were challenged weekly with JR-CSF or REJO.c and monitored for infection.
Results: PBMC humanized mice expressing b12 or VRC01 were protected from intravenous challenge with JR-CSF. In contrast, the b12-resistant REJO.c strain readily infected PBMC humanized mice expressing b12 antibody, while mice expressing VRC01 demonstrated nearly complete protection following challenge. Intravaginally challenged BLT animals expressing luciferase as a control all became infected over the study period while a majority of animals expressing VRC01 or VRC07 had no detectable HIV infection despite repeated intravaginal challenges with JR-CSF or REJO.c.
Conclusion: VIP is capable of protecting humanized mice from challenge by diverse HIV strains and can prevent vaginal transmission. These findings warrant continued development of VIP as a novel approach for HIV prevention.

P02.31 LB

A Single Immunization with Integrase Defective Lentiviral Vector Expressing gp140 Induces Persistent and Functional Immune Response in Rhesus Monkeys

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Background: Integrase defective lentiviral vector (IDLV) expressing antigens induces long-lasting and protective immune responses in mice after a single immunization. IDLV persists at the site of inoculum in the absence of integration, resulting in a prolonged antigen expression. The aim of this study was to demonstrate in monkeys that immunization with IDLV delivering the prototype clade C transmitted founder HIV-1 Env 1086.Cgp140 (IDLV-Env) induces sustained and functional anti-Env antibodies (Abs) and T cell responses.
Methods: Six rhesus monkeys were primed with IDLV-Env and boosted at 1 year after priming. An analysis of Ab response was assessed over time. Binding, epitope mapping, neutralizing activity and ADCC of anti-Env Abs were evaluated at sequential time points. IFNg ELISPOT was performed to evaluate persistence and presence of functional Env-specific T cells.
Results: A single immunization with IDLV-Env induced strong and prolonged immune responses. Anti-Env Abs peaked between 2 and 6 weeks and were still present at 1 year after the vaccination. All monkeys showed neutralizing Abs in serum samples starting from 6 weeks and peaking at 14 weeks after immunization. Three out of 6 monkeys showed ADCC in serum samples and 4 out of 6 had detectable anti-V1V2 Abs. High levels of IFNg producing T cells were elicited in all monkeys, decreasing over time, but still detectable up to 1 year after immunization. Abs and T cell responses showed a significant increase after the boost.
Conclusion: This is the first demonstration that an IDLV-based vaccine expressing HIV Envelope is able to induce functional, comprehensive and persistent immune responses in non-human primates. These results support the further evaluation of IDLV as a delivery system in the context of a HIV-1 vaccine.

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Viral Evolution Following Infection with a Derivative of SHIV1157ipd3N4 Sensitive to V2-Dependent, QNE-Specific, Broadly Neutralizing Antibodies

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Background: PG9 and PG16 are founding members of a class of broadly neutralizing antibodies (BNAbs) that target V2-dependent quaternary neutralization epitopes (QNEs) that includes the conserved N-linked glycan at position N160. CAP256 sera contain related highly potent BNAbs that target an overlapping epitope not dependent on N160. Commonly used SHIVs (SHIV-SF162P3, SHIV-1157ipd3N4, SHIV-AD8, and SHIV-BaL) poorly express these epitopes. Two changes in SHIV-1157ipd3N4 Env, Q170K and I192R, conferred sensitivity to QNE-specific NAbs. This mutant is infectious and pathogenic in pigtail macaques.
Methods: Tracking the course of infection with SHIV1157+QNE should allow the recapitulation of steps leading to the production of QNE-specific BNAbs. We monitored the development of antibody responses and evolution of Env sequences in infected macaques. SGA was used to amplify sequences; representative sequences were cloned for analysis of neutralization sensitivity.
Results: Autologous neutralizing antibodies were detected at week 16 post-infection (PI). At week 16 PI, 12/13 sequences contained mutations at position K143 that conferred resistance to sera from weeks 16 - 32 PI. These viruses were sensitive to week 35 sera, indicating the development of a new antibody response. At week 24, only ~half of the sequences had K143 mutations, and the remaining had V1 deletions and mutations elsewhere in Env, including the K169E mutation that in other Env contexts conferred resistance to neutralization by PG9, PG16, and CAP256 sera.